

ABSTRACT OF THE DISCLOSURE

Assays are presented for screening for chemicals which affect the binding between proteins comprising an SH3 binding motif and nuclear receptor proteins. PNRC (Proline-rich Nuclear Receptor Co-regulatory protein) is a co-regulatory protein comprising an SH3 binding motif and was identified using bovine SF1 as the bait in a yeast two-hybrid screening of a human mammary gland cDNA expression library. This nuclear receptor coactivator binds to several nuclear receptors including those which regulate the aromatase gene which is involved in breast cancer. Compounds which affect the binding of PNRC to nuclear receptors can affect the expression of the aromatase gene as well as of other genes whose expression is under the control of nuclear receptors to which PNRC binds. PNRC is unique in that it has a molecular weight of 35 kDa, significantly smaller than most of the co-regulatory proteins reported so far, and it is proline-rich. In yeast two-hybrid assays, PNRC interacted with the orphan receptors SF1 and ERR α 1 in a ligand-independent manner. PNRC was also found to interact with the ligand-binding domains (LBDs) of all the nuclear receptors tested including ER, AR, PR, TR, RAR, and RXR in a ligand-dependent manner. A 23-amino acid region, aa 278-300, in the carboxy-terminal region was shown to be critical and sufficient for the interaction with nuclear receptors. This region is proline-rich and contains an SH3-binding motif, S-D-P-P-S-P-S (SEQ ID NO:5).

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